ORIGINAL ARTICLE

The incidence of inherited metabolic disorders in the West Midlands, UK

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Background: Inherited metabolic disorders (IMDs) are a heterogeneous group of genetic conditions mostly occurring in childhood. They are individually rare but collectively numerous, causing substantial morbidity and mortality.
Aims: To obtain up-to-date estimates of the birth prevalence of IMDs in an ethnically diverse British population and to compare these estimates with those of other published population-based studies.
Methods: Retrospective data from the West Midlands Regional Diagnostic Laboratory for Inherited Metabolic Disorders (Birmingham, UK) for the 5 years (1999–2003) were examined. The West Midlands population of 5.2 million is approximately 10% of the UK population. Approximately 11% of the population of the region is from black and ethnic minority groups compared with approximately 8% for the the UK.
Results: The overall birth prevalence was 1 in 784 live births (95% confidence interval (CI) 619 to 970), based on a total of 396 new cases. The most frequent diagnoses were mitochondrial disorders (1 in 4929; 95% CI 2776 to 8953), lysosomal storage disorders (1 in 5175; 95% CI 2874 to 9551), amino acid disorders excluding phenylketonuria (1 in 5354; 95% CI 2943 to 9990) and organic acid disorders (1 in 7962; 95% CI 3837 to 17 301). Most of the diagnoses (72%) were made by the age of 15 years and one-third by the age of 1 year.
Conclusions: These results are similar to those of the comparison studies, although the overall birth prevalence is higher in this study. This is probably due to the effects of ethnicity and consanguinity and increasing ascertainment. This study provides useful epidemiological information for those planning and providing services for patients with IMDs, including newborn screening, in the UK and similar populations.

Inherited metabolic disorders (IMDs) are a complex and heterogeneous group of monogenic disorders, usually resulting from deficient activity in a single pathway of intermediary metabolism.[1] Clinical consequences of IMDs are often severe, and they are an important cause of morbidity and mortality in clinical practice, especially in paediatrics.[2]

Although each disorder is individually rare, their cumulative incidence is substantial; an incidence of 1 in 2500–5000 live births is often quoted.[2 3] However, most published studies have focused on specific disorders or groups of disorders, disorders that are screened for or diagnosed in specialist reference laboratories, or in selected populations at particularly high risk for certain conditions.[4–11] Although the results of these studies have shown a high level of consistency, a lack of accurate epidemiological data creates difficulties for those seeking to plan and provide appropriate clinical services for these patients. This is becoming more relevant because of new laboratory technologies for diagnosis and screening and the availability of new (and often expensive) treatment options.[8 12–18] As a result, more patients are now surviving into adulthood, with important consequences for their health and health services.

We therefore aimed to obtain up-to-date estimates of the birth prevalence of IMDs in an ethnically diverse British population and to compare these with other published population-based studies of their prevalence. Substantial changes in ethnic populations in the UK deem that those planning and providing services should have a comprehensive and recent estimate of the potential disease burden. A previous study in the West Midlands reported data that are now over 15 years old.[11] Since 1991 (the final year of data reported in the West Midlands ethnicity study), the proportion of people belonging to minority ethnic groups in the UK has risen by 53% (an increase of 1.6 million people) and that in the West Midlands by over 40% (an increase of 129 510 people). As the incidence of IMDs is around 10 times higher in these minority ethnic groups, this increase has important implications for service provision. Also, the previous study was incomplete because it included only a selection of disorders, excluding urea cycle, organic acid and glycogen storage disorders altogether. Specific ''indicator'' disorders were chosen to represent other IMD groups—for example, medium-chain acyl coenzyme A dehydrogenase deficiency was used to represent fatty acid oxidation disorders. Thus, this new study provides more comprehensive and recent data than the previous study.

METHODS

Retrospective data from the West Midlands Regional Diagnostic Laboratory (Birmingham, UK) were examined for the five most recent years (1999–2003) to mitigate the effects of time trends in awareness and detection, and to enable us to use the most recent data from the 2001 UK census.[19] The study population comprised residents of the West Midlands health region, the largest health region in the UK. The population of 5.2 million accounts for almost 10% of the total UK population; approximately 11% of the population is from black and ethnic minority groups, compared with around 8% for England and Wales.[19] Only data from patients residing within the region were included in the analysis. Individual disorders were grouped into categories, based on the International Classification of Diseases, 10th revision, so

Abbreviations: IMD, inherited metabolic disorders; PKU, phenylketonuria

that the effect of small numbers of individual disorders could be minimised:

- Amino acid disorders (including phenylketonuria, PKU)
- Urea cycle disorders
- Carbohydrate disorders (excluding glycogen storage disorders)
- Carbohydrate disorders (glycogen storage disorders)
- Lysosomal storage disorders
- Mitochondrial disorders
- Purine and pyrimidine disorders
- Peroxisomal disorders
- Lipid and steroid disorders
- Metal disorders
- Fatty acid oxidation disorders
- Organic acid disorders

With the exception of PKU, the data are based on a definitive diagnosis resulting from the investigation of a patient with a clinical problem. Data on PKU were obtained from the Neonatal Screening Programme for the same population and for the same study period. Data on porphyrias, purine and pyrimidine disorders are likely to be incomplete because most diagnoses were made in other reference laboratories. The lipid and steroid category includes only steroid sulphatase deficiency and the Smith–Lemli–Opitz syndrome; diagnoses of the other major endocrine and lipid disorders (such as familial hyperlipidaemia) are made elsewhere, and usually in adulthood. Some disorders of metal metabolism (in particular, Wilson's disorder) are more likely to be made in non-specialist laboratories and in adult age groups. Apart from these specific exceptions, the diagnoses for the other IMD groups are probably complete because the West Midlands laboratory is the only laboratory for this population. Diagnoses of mitochondrial disorders were established either from specific DNA genotypes or from tissue electron transport chain assays of the respiratory chain complexes.

We have used the methods described by Meikle and Dionisi-Vici to define and calculate the birth prevalence as an estimate of incidence.[7 10] Birth prevalence is calculated by dividing the number of diagnoses by the number of live births for a defined time period, assuming that the rate of postnatal diagnosis is equal to the birth rate for each disorder (complete ascertainment).[10] Although this assumption has its problems, it is consistent with the approach adopted in the other comparison studies.[5 7 9–11] The results have been expressed as the reciprocal of the rate; for example, a rate of 0.0001 is expressed as 1 in 10 000.[10] Population and birth statistics were obtained from the Office of National Statistics Online, using data from the 2001 census and FM1 Live Births Series, respectively.[19]

RESULTS

The total number of live births during the study period 1999–2003 was 310 510, and a total of 396 new diagnoses were made (including PKU). Table 1 shows the overall results. The birth prevalence was 1 in 784 live births (95% confidence interval (CI) 619 to 970). The most frequent diagnoses were mitochondrial disorders (1 in 4929; 95% CI 2776 to 8953), lysosomal storage disorders (1 in 5175; 95% CI 2874 to 9551), amino acid disorders excluding PKU (1 in 5354; 95% CI 2943 to 9990), organic acid disorders (1 in 7962; 95% CI 3837 to 17 301) and fatty acid oxidation disorders (1 in 12 938; 95% CI 5123 to 35 971). If these results were extrapolated to the total number of annual live births in the UK population, there would be approximately 800 new diagnoses made each year.

Table 2 shows a comparison of the results with those of the other published international studies. Although the overall birth prevalence is higher in the West Midlands, the results are reasonably consistent across disorder subgroups, especially for PKU, which is universally screened for in the newborn period in each of these countries.

Table 3 shows the age at diagnosis for six major disorder classes, on the basis of the classification used in the Italian and Canadian studies.[9 10] Age data were not available for 34 patients (13% of the total). Most disorders (72%) were diagnosed by the age of 15 years, 56% by the age of 5 years and 35% by the age of 1 year. Only a quarter of diagnoses were made after the age of 15 years. Patients with small-molecule disorders and carbohydrate disorders were generally diagnosed in the neonatal period, with lysosomal storage disorders being diagnosed principally in infancy and early childhood. Diagnoses of mitochondrial disorders were generally made in adulthood.

Table 1 Frequency of inherited metabolic disorders in the West Midlands, 1999–2003

Condition	Total number of cases	Birth prevalence (live births)	Lower 95% CI	Upper 95% CI
PKU*	25	1 in 12 420	5008	33 784
Amino acid (excluding PKU)	58	1 in 5354	2943	9990
Urea cycle defects	14	1 in 22 179	6702	90 909
Carbohydrate	19	1 in 16 343	4509	52 910
Organic acid	39	1 in 7962	3837	17 301
Glycogen storage	21	1 in 14 786	5504	44 643
Lysosomal storage	60	1 in 5175	2874	9551
Purine and pyrimidine†	4	1 in 77 628	12 063	2 000 000
Fatty acid oxidation	24	1 in 12 938	5123	35 971
Peroxisomal	23	1 in 13 500	5244	38 462
Mitochondrial	63	1 in 4929	2776	8953
Metals†	11	1 in 28 228	7418	147 059
Lipids and steroids‡	20	1 in 15 526	5647	48 544
Porphyrin and haem§	1	1 in 310 510	10 070	3 333 333
Miscellaneous	14	1 in 22 179	6702	90 909
Total (including PKU)	396	1 in 784	619	970

*Data included from the Neonatal Screening Programme.
†Incomplete, as some diagnoses are made in non-specialist laboratories.
‡Includes only steroid sulphatase disorders and Smith–Lemli–Opitz syndrome.
§Incomplete, as diagnosis is usually made in supra-regional centres.
PKU, phenylketonuria.

Table 2 Comparison of the birth prevalence of IMDs in published population-based studies with that in developed countries

	West Midlands (this study)	Italy*	West Midlands ethnicity study	Canada (British Columbia)†
Year published	2005	2002	1998	2000
Primary study period for reported results	1999–2003	1993–97 (data collected from 1985 to 1997)	1981–91	1969–96 (time period varies for each disorder)
Number of patients	396	1935	263	249
Disorder groups				
Amino acid	1 in 5354	1 in 36 389*		1 in 6606
PKU	1 in 12 420	1 in 19 589‡	1 in 14 452 (Pakistani); 1 in 12 611 (white)	1 in 13 290
Carbohydrates	1 in 16 343	1 in 19 532		
Urea cycle	1 in 22 179	1 in 41 506		
Glycogen storage	1 in 14 786	1 in 34 056		1 in 43 160 1 in 69 054
Lysosomal storage	1 in 5175	1 in 8275		1 in 13 112
Mitochondrial	1 in 4929			1 in 31 436
Peroxisomal	1 in 13 500	1 in 71 794		1 in 28 960
Organic acids	1 in 7962	1 in 21 422		1 in 27 082
Total	1 in 784	1 in 3707 (1985–97) 1 in 2758* (1993–97) 1 in 2555 (1993–97)	1 in 2691 1 in 318 (Pakistani); 1 in 3760 (white)	1 in 2500†

*Excluding PKU (phenylketonuria).
†Excludes disorders of collagen, metal, lipids and porphyria.
‡Data from the Italian National Neonatal Screening Survey.[10]

DISCUSSION

We have estimated that the birth prevalence of IMDs in the West Midlands is 1 in 784 for the years 1999–2003. This is the only recent published estimate from an ethnically diverse UK population, and is higher than the often-quoted estimate of 1 in 2500–5000 live births. Extrapolating these results to the total UK population would suggest approximately 800 new diagnoses each year. Most (72%) patients with IMDs are diagnosed by the age of 15 years, with one-third diagnosed by the age of 1 year.

These results are broadly similar to those of the comparison studies, although a number of factors need to be considered when interpreting these results. Some cases of IMD will be unidentified because of deaths occurring before a diagnosis is made. Completeness of ascertainment is affected by many factors, including the ease of diagnosis, the presence of screening programmes, whether diagnostic laboratories and associated clinical services have specific clinical interests or specialist practitioners, and whether patients are referred to other specialist centres for investigation and treatment. For example, the West Midlands regional service has a particular interest in tyrosinaemia and mitochondrial disorders, and has only recently appointed a specialist metabolic paediatrician. The potential effect of screening programmes is shown in the Italian study, where the birth prevalence of galactosaemia was 2.6 times as higher in areas with a screening programme.[9]

Another important issue is the effect of ethnicity and consanguinity on the incidence of metabolic disorders. The proportion of people belonging to ethnic minority groups in the Canadian study was around 6% compared with 11% for the West Midlands, and the Italians reported that their study population had a low consanguinity rate and that other ethnic communities were small.[9 10] Although the ethnic diversity does not affect the validity of our results, it limits comparisons with less ethnically diverse populations. It is probably the single most important reason for the higher overall birth prevalence in our study, especially as the

Table 3 Age at diagnosis for the major classes of metabolic disorder

Age at diagnosis	Small-molecule disorders,• n (%)†	Carbohydrate disorders,‡ n (%)	Lysosomal storage disorders, n (%)	Peroxisomal disorders, n (%)	Mitochondrial disorders, n (%)	Other disorders, n (%)	Cumulative percent
<4wk	37 (29)	12 (33)	2 (3)	4 (18)	3 (5)	1 (2)	16
4wk–11 mo	21 (16)	7 (19)	17 (29)	4 (18)	2 (3)	19 (34)	35
1–4 y	31 (24)	10 (28)	23 (40)	2 (9)	6 (10)	5 (9)	56
5–9 y	6 (5)	2 (6)	3 (5)	6 (27)	1 (2)	9 (16)	63
10–14 y	6 (5)	2 (6)	5 (9)	1 (5)	5 (8)	14 (25)	72
15–19 y	2 (2)	0 (0)	3 (5)	0 (0)	3 (5)	5 (9)	76
20–24 y	1 (1)	0 (0)	0 (0)	0 (0)	3 (5)	0 (0)	77
25–29 y	6 (5)	0 (0)	0 (0)	2 (9)	9 (15)	2 (4)	82
30–34 y	4 (3)	0 (0)	0 (0)	1 (5)	4 (6)	0 (0)	84
35–39 y	2 (2)	0 (0)	1 (2)	0 (0)	3 (5)	0 (0)	87
40–44 y	5 (4)	0 (0)	0 (0)	0 (0)	3 (5)	0 (0)	88
45–49 y	3 (2)	0 (0)	3 (5)	0 (0)	3 (5)	1 (2)	91
50–54 y	1 (1)	1 (0)	1 (2)	2 (9)	6 (10)	0 (0)	94
55–59 y	1 (1)	2 (6)	0 (0)	0 (0)	6 (10)	0 (0)	96
60–64 y	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	97
65–69 y	2 (2)	0 (0)	0 (0)	0 (0)	3 (5)	0 (0)	99
>70 y	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	100
Total	128 (100)	36 (100)	58 (100)	22 (100)	62 (100)	56 (100)	362

*Includes amino acid, organic acid, fatty acid oxidation and urea cycle disorders.
†All percentages rounded.
‡Includes glycogen storage disorders.
mo, months; wk, weeks; y, year.

What is already known on this topic

- Although inherited metabolic disorders (IMDs) are individually rare, their cumulative incidence is substantial: a birth prevalence of 1 in 2500–5000 live births is often quoted.

What this study adds

- This study provides recent epidemiological data from an ethnically diverse UK population and is useful to those providing and planning services for patients with IMDs.
- In the five years from 1999–2003, the birth prevalence was 1 in 784 live births, substantially higher than previously quoted estimates. This translates to around 800 new cases per year in the UK as a whole.

proportion of people belonging to minority ethnic groups has increased substantially since 1991. Other factors that may explain this discrepancy include differences in diagnostic methods and approaches between laboratories and countries, the use of alternative coding and classification systems, and temporal trends.

The Italian study used the *Online Mendelian Inheritance in Man*[20] system, whereas the Canadian authors did not report which classification system they used; these may have introduced some differences in the way disorders were categorised compared to our study. Both the Canadian and Italian studies reported increases in the number of diagnoses over time. These time trends can be attributed to advances in diagnostic technology, better coverage and reporting, increased awareness and the emergence of knowledge about new disorders (such as mitochondrial disorders). Because our study is the most recent, we would expect higher ascertainment as a result of these factors. These increases probably do not represent a true increase in incidence. A Comparison of the birth prevalence of PKU with that of other metabolic disorders supports this interpretation. Because neonatal screening programmes have been in place for many years in each country, the completeness of ascertainment should be both high and stable. As expected, the birth prevalence statistics are very similar: 1 in 12 240 (our data), 1 in 19 589 (Italy) and 1 in 13 290 (Canada); most of the variation is in the other disorders, which will have more variable levels of ascertainment. Many of these disorders are extremely rare, and random variation in their incidence is high (reflected in the width of CIs). Hence the diagnosis of even one more case over a short time period may have an important effect on the birth prevalence of certain disorders. Once these factors are taken into account, the birth prevalence estimates are remarkably consistent between studies.

This study emphasises the important role of the laboratory in obtaining such data. The analysis was made possible only because of accurate recording by a specialist laboratory, serving a defined population, by disorder and by geographical area, over a period of time. We believe that such an approach should be extended across the whole of the UK in the form of a national register. In the meantime, these data should prove helpful in the planning and provision of services for patients with IMDs, particularly in areas with a similar, ethnically diverse population.

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